REMARKS

I. Status of the Claims

By the present communication, claims 1, 2, 5, and 13-15 are amended to recite "gaseous propellant." Support for the amendment may be found at paragraphs 21-22 of the (published) specification as filed, and thus no new matter is added. Claims 1-19 and 23 remain pending and under examination in this application. Applicant respectfully requests reconsideration of the present application in view of the foregoing amendment and the reasons that follow.

II. Claim Rejections – 35 U.S.C. § 103

Claims 1-19 and 23 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over U.S. Pat. No. 6,135,628, issued to DeStefano *et al.* Claims 1-19 and 23 also stand rejected under 35 U.S.C. § 103(a), as being unpatentable over U.S. Pat. No. 6,228,346, issued to Zhang *et al.* in view of WO 0025746, by Bernini *et al.* In support of these rejections, the Office argues that

> [T]he features upon which applicant relies (i.e., a gaseous state) are not recited in the rejected claims(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. The claims require that the active agent being suspended in a gas propellant. The claims do not require that the suspension be in a gaseous state. ... The instant claims also employ the open-ended transitional term "comprising" which allows for the presence of non recited components or features. (*Office Action dated 1/21/2011, p. 14, lines 3-12, citations omitted*)

Applicant respectfully traverses these rejections for the following reasons.

(A) DeStefano does not teach or suggest all limitations of the claimed process

As an initial matter, Applicant notes that the claims are amended to recite "gaseous propellant." Support for this amendment is found in the definitions of "propellant" and "suspension" provided in the application. The specification teaches at paragraph 21 of the

published application that "another class of compressed gases are propellants, including hydrofluoroalkanes." That these propellants are compressed gases rather than liquefied gases is clear from the disclosure in the specification, including the definition of "suspension" provided. "For the purpose of the invention 'suspension' means a two phase system consisting of a finely divided solid dispersed in a continuous, e.g. compressed, gas phase." (Paragraph 22, emphasis added.) As used in the claims, "suspension" does not mean a dispersion of solids in a liquid phase as suggested by the Office as such a definition is inconsistent with the definition of the specification. Thus, this is not a case where Applicant is arguing limitations not recited in the claims; the term "suspension" is recited by the claims, and, because Applicant may be his own lexicographer (see MPEP 2111.01 IV, and cases cited therein), the definition provided by the specification excludes a liquid phase suspension.

A prima facie case of obviousness requires the Office to demonstrate that all claim limitations may be met by the prior art or a modification of prior art within the ordinary skill in the art. As explained above, the present claims recite that the active agent should be suspended in a gaseous propellant. Conversely, DeStefano clearly states that his claimed homogenizer will micronize organic pharmaceutical compounds which are suspended in a liquid (DeStefano, Col. 5, line 66-Col. 6, line 1). DeStefano fails to teach the micronization of a suspension of a pharmaceutically active agent in a continuous gas phase. Applicant's use of the transitional phrase "comprising," does not somehow make up for the lack of this element in DeStefano as implied in the Office Action.

Furthermore, the Office fails to point to any teaching in DeStefano of a micronization process wherein the dry micronized powder of the pharmaceutically active agent can be obtained directly upon depressurization, as in the presently claimed process. Claims 3 and 4 further distinguish over DeStefano by reciting micronized particle sizes of between about 0.1 and about 7.0 micrometers and from about 0.5 to about 5.0 micrometers, respectively. DeStefano teaches in Comparative Example 4 that particles were produced having sizes in the range of 12 μm to 15 μm (col. 15, lines 9-10). Thus, DeStefano, fails to teach each element of the claims. As shown

below, the Office has also failed to identify reasons to modify the DeStafano or show a reasonable expectation of success in doing so.

(B) There is no reason to modify the process taught by DeStefano and there is no reasonable expectation of success for the proposed modification

In the Office Action, the Examiner states that while the reference by DeStefano does not anticipate the instant claims, it discloses every limitation and sufficient teachings to one of ordinary skill in the art to make and use the invention as claimed (Office Action at page 8). Applicant disagrees with this assertion.

First, a reference which does not anticipate cannot teach every limitation of the present claims. As explained in section II(A) above, DeStefano does not disclose suspension of the pharmaceutically active agent in the absence of a liquid phase as part of the micronization process.

Moreover, DeStefano does not provide sufficient teachings or reasons for the skilled artisan to modify the reference and arrive at the presently claimed invention. Absent a principled reason for the skilled artisan to use a gaseous propellant in a manner contrary to the preferences expressed by DeStefano, the reference must fail to support the present rejection. A person skilled in the art looking at DeStefano would not be inspired to use a gaseous propellant in the described process.

Applicant submits that if the person of ordinary skill in the art were presented with the DeStefano reference, that person would understand that the homogenization process requires the active agent to be suspended in a liquid. This is because DeStefano defines "aerosol formulation" as a liquid suspension and repeatedly stresses that precautions must be taken to ensure that the propellants must be liquid in order to avoid vaporization. As pointed out in Applicant's previous response, DeStefano defines an aerosol formulation as "one which comprises a solution or suspension of an active ingredient in a liquid which consists of a propellant and an [sic] any necessary solvent or surfactant." (Col. 1, lines 20-23.) Subsequent

references to such formulations clearly state the concern over keeping the propellants liquid. For example, DeStefano states in Col. 3, lines 1-8, that "homogenization of a formulation comprising a low boiling HFA (hydrofluorocarbon alkane) must either be carried out at elevated pressure or reduced temperature because the low boiling HFA would otherwise evaporate," and in Col. 3, lines 10-13 "rotor/stator homogenizers do not presently exist which are adapted to operate under sufficient pressure to prevent the volatilization of a low boiling constituent, such as a propellant." DeStefano also adds that "[o]nce all of the components of the aerosol formulation are in the mixing vessel 10 and the mixing vessel is pressurized to about 70-80 psi, the aerosol formulation is ready for mixing, homogenization and micronization." Col. 7, lines 1-6. Moreover, the note to the table listing formulation components in column 7 states that the quantity of low boiling solvent (1,1,1,2,3,3,3-heptafluoropropane) used includes some to make up for losses during filling as the "liquid bulk suspension" is depleted. In fact, these constant admonitions to use a liquid suspension of active ingredient teach away from using Applicant's claimed methods which recite forming a suspension in a gaseous propellant or a compressed gas.

Even assuming *arguendo* that a skilled artisan would have thought of modifying DeStefano's process as a "second option," as suggested by the Office, Applicant submits that "a reasonable expectation of success is still a requirement for a *prima facie* case of obviousness" *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360, 83 USPQ2D 1289, 1301 (Fed. Cir. 2007). Such an expectation must be supported by the factual evidence in order to establish a *prima facie* case of obviousness. (MPEP 2142, 1st paragraph, "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness.") This the Office has not done.

The Office does not expressly address the reasonable expectation of success but asserts only that "it would have been obvious to one of ordinary skill in the art to have modified the references by substituting the liquefied gas propellant with a gaseous gas propellant because the options would have been very finite and it would have been obvious for one of ordinary skill to have tested the same process with a second option." Applicant respectfully submits that the

options for improving the methods of DeStefano were not so limited and would include changing the propellant, the temperature, the concentration of the active ingredient and the like rather than the phase of the propellant, given the explicit teaching in DeStefano to maintain the propellant in the liquid phase. As noted above, changing the phase of the propellant to gas rather than a liquid is contrary to DeStafano's teachings and the Office has presented no evidence that a skilled artisan could expect a process using a gas propellant to be equally successful.

(D) Zhang alone or in combination with Bernini does not teach all limitations of the claimed process

The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have implemented the step of high pressure homogenization of Bernini et al. in the processes and formulations of Zhang with a reasonable expectation of successfully preparing dry powder particles in a suitable particle size with the known process of high pressure homogenization (Office Action at page 12).

Applicant submits that like DeStefano above, Zhang fails to teach all limitations of the present claims. Zhang is directed to the providing "improved and environmentally friendly propellants and aerosol formulations which contain them." (Col. 2, lines 39-40.) Zhang teaches mixing, in a liquid state, gases with low evaporation enthalpy with another gas having high evaporation enthalpy. (Col. 3, lines 5-22.) This propellant mixture may be used "for pharmaceutical aerosols so as to micronize the drugs for pulmonary application." (*Id.*, lines 23-26.) "This propellant mixture is present in the *subcritical state*..." (*Id.*, lines 26-30, emphasis added). The skilled artisan understands that the subcritical state for a gas includes the liquid state. In fact, all of the examples describe that the pharmaceutical compound is dissolved in a liquid mixture by maintaining vapor pressure of 5 to 20 bar. Moreover, contrary to the process of present claims 9-10, Zhang specifically teaches away from the use of halogenated hydrocarbons for the micronization process (Col. 2, lines 40-44). As admitted by the Office, Zhang also lacks specific disclosure on the step of high pressure homogenization, a deficiency, which is allegedly cured by Bernini (Office Action at page 11). However, Zhang fails to teach a suspension

comprising a solid pharmaceutically active agent in a continuous gas phase, and Bernini fails to cure this deficiency with respect to the presently claimed invention.

Bernini is directed to the preparation of particle suspensions for use in formulations for aerosol inhalation. *See* page 2, lines 13-15. This is accomplished using a turboemulsifier, which includes a containment vessel equipped with magnetic stirring and a high potency turbine system for homogenizing the suspension. *See* page 2, lines 15-26. Bernini then goes on to describe that the "process includes a first step wherein an *aqueous solution* which constitutes the carrier is dispersed in a turboemulsifier apparatus." *Id.* In a preferred embodiment, the drug is dispersed in the aqueous phase and then is subject to additional homogenization under high pressure. *See* page 3, lines 12-15. Thus, Bernini, like Zhang, and DeStefano above, is directed to suspension in a liquid medium to prepare the aerosol formulation.

Thus, both Zhang and Bernini disclose as an essential step of the process that the pharmaceutically active agent is suspended or dissolved in a liquid phase, and not in a gas propellant, as in the presently claimed process. Moreover, neither of the two references teach that the micronization process enables one to obtain dry micronized powder of the pharmaceutically active agent directly upon depressurization after homogenization, as recited in the present claims. As a result, Zhang and Bernini fail to disclose, suggest, or teach all of the limitations of the claimed processes and, therefore, cannot render the present claims obvious.

(D) The claimed process exhibits unanticipated benefits which are not evident from the teachings of the prior-art

The Office asserts that unless the Applicant demonstrates the criticality of the order of addition and that the prior art is not the same product as the instant application, changes in sequence of adding ingredients has been rendered to be prima facie obvious (Office Action at page 15). Applicant submits that the Examiner's rejections misapprehends the steps of the claimed invention and misstates the legal standards for obviousness. First, the present process does not merely change a sequence of addition, as asserted by the Office. Second, a process can

be nonobvious over and patentably distinct from a prior art process even though it produces the same product.

As discussed above, the presently claimed process is patentably distinct from the process disclosed in the cited references. In the presently claimed micronization process, the pharmaceutical active agent is directly suspended in a gaseous propellant or compressed gas and is processed by high pressure homogenization. On the other hand, DeStefano, Zhang and Bernini disclose processes which require the pharmaceutical compound is dissolved or suspended in liquid phase prior to homogenization.

The presently claimed process exhibits several unanticipated benefits over the teachings and suggestions of the process disclosed in DeStefano, Zhang and Bernini. First, the particle size of the drug substance powder is reduced by the process of the invention to an average particle size of less than about 7 μm (Published Application US 2008/0026981, p. 1, ¶¶ [0006]-[0007]). Conversely, the method disclosed in DeStefano produces particles having sizes within the range of 12 μm to 15 μm (DeStefano, Col. 15, lines 8-9). Products with mean particle diameter of about 17 μm after 180 min of processing time is demonstrated in Fig. 5 of DeStefano. In comparison, much smaller particle size of 2.13 is obtained, after the same processing time of 180 min, using the process of the present invention (*See* Table 2).

It is desirable to obtain particles of low average particle size for use in pulmonary or inhalation formulations. As disclosed in ¶ [0034] of the presently published application, pharmaceutically active agent powder particles of a size of about 1 to about 5 μm may be used for dry powder inhaler (DPI) formulations. Further, as discussed in ¶ [0004] of the presently published application, it is difficult to match the average particle size requirements when micronized powders are produced from techniques such as those using supercritical fluids. The particle size requirement is also emphasized by Zhang in Col. 4, lines 18-26, wherein it is disclosed that "As far as a suspension aerosol is concerned, what is also of consequence is the original particle size of the pharmaceutical to be suspended in the propellant mixture." Since the particle size is indeed (undesirably) increased during the spraying process, but virtually cannot be

reduced in size, the pharmaceutical should already be present in a sufficiently fine form before being introduced into the propellant, i.e., reduced to a particle diameter of less than 8 μm. The fine particles can also be more easily suspended.

Second, the conventional liquid-based processes disclosed in the cited references result in difficulties obtaining a useable, dry powder product upon depressurization because residual liquid from the process must be removed from the pharmaceutically active agent. Moreover, the liquid-phase processes require an additional solvent removal step which adds to the cost of downstream processing. Thus, the process described in the cited references will likely require additional solid-liquid separation and formulation steps such as filtration, evaporation, centrifugation, milling, freeze-drying, spray-drying, lyophilization, etc. Additionally, the downstream process may exhibit a negative effect on the physical and chemical properties of the final product. For example, the high temperatures in processes such as spray–drying may chemically damage the active pharmaceutical ingredient. Likewise, processes such as dry milling increase the amorphous content in particulate formulations of pharmaceutically active agents. Increases in amorphous content are usually disfavored and may even weaken or cause adverse therapeutic effects. Many of these processes are also very expensive on large scale.

On the other hand, the process of the present invention is associated with several benefits which are not achievable using the liquid-based process disclosed in the cited references. For example, the presently claimed process can be used to micronize very adhesive and sticky drug substances and high-aspect ratio, spicular or needle-like crystals. Moreover, the process provides ease of operation and is economical because the suspension of the pharmaceutically active agent can be micronized in a single step process and a dry powder of the pharmaceutically active agent is directly obtained upon depressurization. This powder can be used in various formulations, such as, for example, inhalation formulation, without any further processing. An additional advantage is that the process can be conducted under milder and inert reaction conditions and avoids the use of solvents, increase of amorphous content, contamination and attrition. The claimed process is thus beneficial in terms of requiring no downstream processing to remove

solvent, no degradation and no risk of elevated amorphous content (Published Application, p. 1, ¶¶ [0003], [0004], [0009] and [0034]).

Finally, the use of gas as propellant in the process of the present invention, allows, 1) a more flexible use of high-pressure homogenization devices tailored for the micronization problem at hand (i.e., use of dynamic valves instead of static interaction geometries); and 2) a broader range of application with respect to solids loading, which may clog equipment in conventional Microfluidizer operation; and a single, as well as a two-vessel operation concept, that allows a more efficient control of the average particle size by more stringently controlling the residence time through the number of passes through the equipment (Published Application, ¶¶ [0025]-[0029]). None of the processes disclosed in DeStefano, Zhang or Bernini would allow such flexibility of operation.

Because the cited references do not teach each element of the claims, because DeStafano in fact teaches away from forming a suspension of active pharmaceutical ingredient in a gaseous propellant or compressed gas as part of a high pressure micronization proces, because the Office has not established a reasonable expectation of success would result from modification of the prior art method, the Office has failed to establish a *prima facie* case of obviousness. In addition, the claimed methods offer significant advantages over the prior art methods as a solution to problems not recognized by the prior art. Accordingly the claimed invention is nonobvious; withdrawal of this ground of rejection is respectfully requested.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit

card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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